Pharmacometrics Consult Review	
BLA	BLA 125771.0
Submission Type	Original submission
Submission Date:	June 30, 2022
Applicant:	Bioverativ Therapeutics Inc
Brand Name:	ALTUVIIIO
Generic Name:	Antihemophilic Factor (Recombinant), Fc-VWF-XTEN Fusion Protein
ClinPharm Reviewer:	Xiaofei Wang
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OCP Division:	CBER Office of Tissues and Advanced Therapies – Consult Request to DPM

1. BACKGROUND

ALTUVIIIO [recombinant coagulation factor VIII Fc-von Willebrand factor–XTEN fusion protein] is a new class of factor VIII (FVIII) replacement therapy indicated for the treatment and control of bleeding episodes occurring in adults and children with hemophilia A (congenital factor VIII deficiency) based on the mean annualized bleed rate (ABR) of routine prophylaxis and on-demand treatment in Study XTEND-1 (EFC16293) being 0.71 (95% CI: 0.52-0.97) and 21.4 (95% CI: 18.8, 24.4), respectively, for a weekly dose of 50 IU/kg. The drug product is a sterile, latex free, lyophilized dosage form that is reconstituted with sterile water for injection prior to administration by the intravenous route. The applicant seeks approval of routine prophylaxis, on-demand treatment, and perioperative management using ALTUVIIIO in adults and children based on Study XTEND-1 in adults and adolescents (12 years and older) and the ongoing Study XTEND-Kids (EFC16295) in pediatrics under 12 years.

In the ongoing Study XTEND-Kids, the ABR for a weekly dose of 50 IU/kg was 0.28 (95% CI: 0.07-0.12) and 0.76 (0.27-2.16) for children < 6 years and 6 to <12 years, respectively, based on an interim analysis (data cutoff date of 24 January 2022). For both age cohorts, the ABR is consistent with that observed in adults.

2. EXECUTIVE SUMMARY

Population PK (popPK) analysis suggests that the exposure of ALTUVIIIO at steady state was lower in pediatrics younger than 12 years compared to adults and adolescents receiving 50 IU/kg weekly dose. This is due to a less than proportional shift in CL with body weight when dose is scaled linearly by body weight. The Cmax,ss and Ctrough,ss of ALTUVIIIO were about 19-24% and 46-63% lower, respectively, in pediatric patients younger than 12 years relative to adult patients.

PK/PD analysis was conducted using adult and adolescent data from XTEND-1 which described a negative relationship between FVIII activity and bleeding risk. Based on modeling and simulation, maintaining FVIII activity >40 IU/dL for a dosing interval is expected to deliver an optimal effect in reducing the bleeding risk; meanwhile, maintaining FVIII activity >20 IU/dL for a dosing interval is deemed sufficient.

With the recommended dose for routine prophylaxis, the average fractions of time >40 IU/dL FVIII activity for a dosing interval are 58% and 49%, and the average fractions of time >20 IU/dL FVIII activity for a dosing interval are 89% and 77%, for adults and adolescents, respectively. Therefore, a near plateaued clinical efficacy is achieved in adult and adolescent patients receiving 50 IU/kg ALTUVIIIO weekly.

In pediatrics younger than 12 years, the average fractions of time >40 IU/dL FVIII activity for a dosing interval are 43% and 35% for 6-<12 years and <6 years age cohort, respectively, and the average fractions of time >20 IU/dL FVIII activity for a dosing interval are 70 and 59%, for 6-<12 years and <6 years age cohort, respectively. While FVIII activity is only maintained above 40 IU/dL for 35-43% of a dosing interval, the effect in bleeding prevention could still be adequate since the FVIII activity above >20 IU/dL is maintained for majority of a dosing interval.

Despite a shorter expected duration above FVIII targets in pediatric patients compared to adults, the bleeding prevention in pediatrics younger than 12 years is predicted to be better than the accepted treatment goal of an approved FVIII replacement therapy, Eloctate. The interim results of the ongoing XTEND-Kids also showed a comparable ABR in these patients to that observed in adults and adolescents despite a reduced FVIII activity. Taken together, the prophylactic dosage of 50 IU/kg weekly in pediatrics is considered adequate for bleeding prevention based on model prediction and clinical observations.

3. Labeling Recommendation

- Routine prophylactic dose in pediatrics less than 12 years of age same as adults.
- In pediatrics less than 6 years of age, a more frequent (5 days intervals) or a higher dose (80 IU/kg) is predicted to achieve similar exposure as adults. We defer the inclusion of upper limits in the label to clinical reviewer for an optional dose escalation or intensification in pediatrics when necessary.
- Based on FVIII pharmacokinetic/pharmacodynamic (PK/PD) analyses, the risk of bleeding is negatively correlated with FVIII activity.

4. RECOMMENDATION

The Office of Pharmacometrics has reviewed the information contained in BLA 125771.0. This submission is approvable from pharmacometrics perspective.

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5. QUESTION BASED REVIEW

5.1 Dose the Pharmacometrics finding support the proposed dose in pediatric patients younger than 12 years old?

The results from modeling and simulations support 50 IU/kg weekly prophylactic regimen in pediatric patients.

The popPK model of ALTUVIIIO was developed using plasma one-stage FVIII activity data of Phase 1~3 studies inclusive of adult, adolescent, and pediatric patients (refer to ***Appendix 6.1*** for details of the popPK model). Based on modeling and simulation, the predicted half-life is 44 hours in 6-<12 years age cohort and 40 hours in <6 years age cohort, which was comparable to the half-life derived from NCA analysis (**Table *1***).

Table 1. Steady State FVIII Activity in Adults and Pediatrics Treated with 50 IU/kg ALTUVIIIO Once Weekly

Age group	Post-hoc PK parameters from popPK				PK parameters from NCA			
	N	CL (mL/h/kg)	V (mL/kg)	T1/2 (h)	N	CL (mL/h/kg)	Vss (mL/kg)	T1/2 (h)
<6 years	14	0.82 (0.12)	48 (8.5)	40 (3.8)	14	0.74 (0.13)	38 (7.2)	40 (5.7)
6-<12 years	18	0.73 (0.093)	47 (5.9)	44 (3.4)	18	0.68 (0.14)	38 (6.8)	42 (3.7)
12-<18 years	25	0.64 (0.10)	44 (7.0)	48 (5.0)	25	0.58 (0.12)	35 (7.4)	45 (5.0)
≥18 years	134	0.53 (0.11)	39 (5.2)	52 (8.9)	128	0.49 (0.12)	31 (7.3)	48 (9.3)

Source: Applicant's PopPK report (Table 18). Values expressed as MEAN (SD). NCA: non-compartmental analysis.

The bleeding events in adult and adolescent patients dosed with ALTUVIIIO were well described by a repeated time-to-event model (RTTE) whose base hazard was best characterized by a Weibull function. The base hazard was reduced by FVIII activity in an exposure dependent manner at the therapeutic range (refer to ***Appendix 6.2*** for details of the RTTE model). The predicted probability of first bleed in 1 year indicated that maintaining FVIII activity >40 IU/dL would achieve a plateaued effect for bleeding prevention during a dosing interval. Such effect is near plateau when FVIII activity is maintained > 20 IU/dL (**Table *2***).

Table 2. Probability of First Bleed in 1 Year in a Typical Patient and ABR in Virtual Population for ALTUVIIIO and Eloctate for Continuous Infusion Regimens

Compound	Dosing regimen (IU/kg/week[a])	Constant FVIII activity at steady state (IU/dL)	Probability of first bleed in 1 year (95% CI) in a typical patient[b]	Annualized bleed rate (ABR) in virtual population (N=1000)	
				Mean (SD[c])	Median (IQR[c])
BIVV001	18.6	20	0.45 (0.29, 0.68)	1.2 (2.4)	0 (0, 1)
	23.2	25	0.39 (0.24, 0.62)	0.99 (2.0)	0 (0, 1)
	27.9	30	0.34 (0.19, 0.56)	0.84 (1.6)	0 (0, 1)
	32.5	35	0.30 (0.16, 0.52)	0.64 (1.3)	0 (0, 1)
	37.2	40	0.27 (0.14, 0.48)	0.66 (1.4)	0 (0, 1)
Eloctate	79.9	20	0.48 (0.37, 0.60)	1.0 (1.7)	0 (0, 1)
	100	25	0.43 (0.32, 0.55)	0.86 (1.4)	0 (0, 1)
	119.9	30	0.38 (0.28, 0.50)	0.84 (1.5)	0 (0, 1)
	139.8	35	0.35 (0.24, 0.47)	0.65 (1.1)	0 (0, 1)
	159.8	40	0.32 (0.21, 0.44)	0.61 (1.1)	0 (0, 1)

[a]Drug was dosed as continuous infusion over 1 week.
[b]For BIVV001 the typical patient has bodyweight of 78.3 kg; for Eloctate the typical patient has bodyweight of 73 kg, VWF of 118 IU/dL and hematocrit of 45%.
[c]Simulated IQR is 25th percentile to 75th percentile. CI is confidence interval and SD is standard deviation
[d]The data needs careful interpretation as dosing regimen is hypothetical and doses simulated were not tested in the clinical studies.

Source: Applicant's IR response dated 11/18/2022 (Table 1).

In pediatric patients younger than 12 years administered 50 IU/kg ALTUVIIIO weekly, the fraction of time above the FVIII activity targets is shorter than that in adult and adolescent patients who received the same dose (**Table *3***). The average fractions of time >40 IU/dL and >20 IU/dL FVIII activity for a dosing interval are 35%-43% and 59-70% for pediatrics of <6 years and 6-<12 years age cohort, respectively; the corresponding values are 49%-58% and 77-89%, for adolescents and adults, respectively. While a maximal response could not be attained with the current dosage in either adults or pediatrics, FVIII activity >20 IU/dL is largely maintained for a dosing interval in adults and adolescents, and to a lesser extent but still for a significant portion of a dosing interval in pediatrics younger than 12 years.

Table 3. Steady State FVIII Activity in Adults and Pediatrics Treated with 50 IU/kg ALTUVIIIO Once Weekly

PK Parameters	1 to <6 years	6 to <12 years	12 to <18 years	Adults
	N = 20	N = 35	N = 24	N = 124
Peak (IU/dL)	113 (26.2)	121 (25.31)	124 (31.2)	150 (35.0)
Trough (IU/dL)	6.75 (2.29)	9.77 (3.64)	9.23 (4.77)	18.0 (16.6)
Time to 40 IU/dL (h)	59.2 (7.68) [35%]	72.2 (11.2) [43%]	81.7 (13.1) [49%]	97.0 (20.2) [58%]
Time to 20 IU/dL (h)	99.3 (9.15) [59%]	117 (13.9) [70%]	130 (15.7) [77%]	150 (31) [89%]
Time to 10 IU/dL (h)	139 (11.7) [83%]	163 (17.1) [97%]	179 (21.4) [107%]	200 (35.4) [119%]

Source: Applicant's PopPK report (Appendix 14) and clinical overview (Table 2). Values expressed as MEAN (SD) for peak and trough. Values expressed as MEAN (SD) [Fraction of dosing interval] for time to FVIII activities.

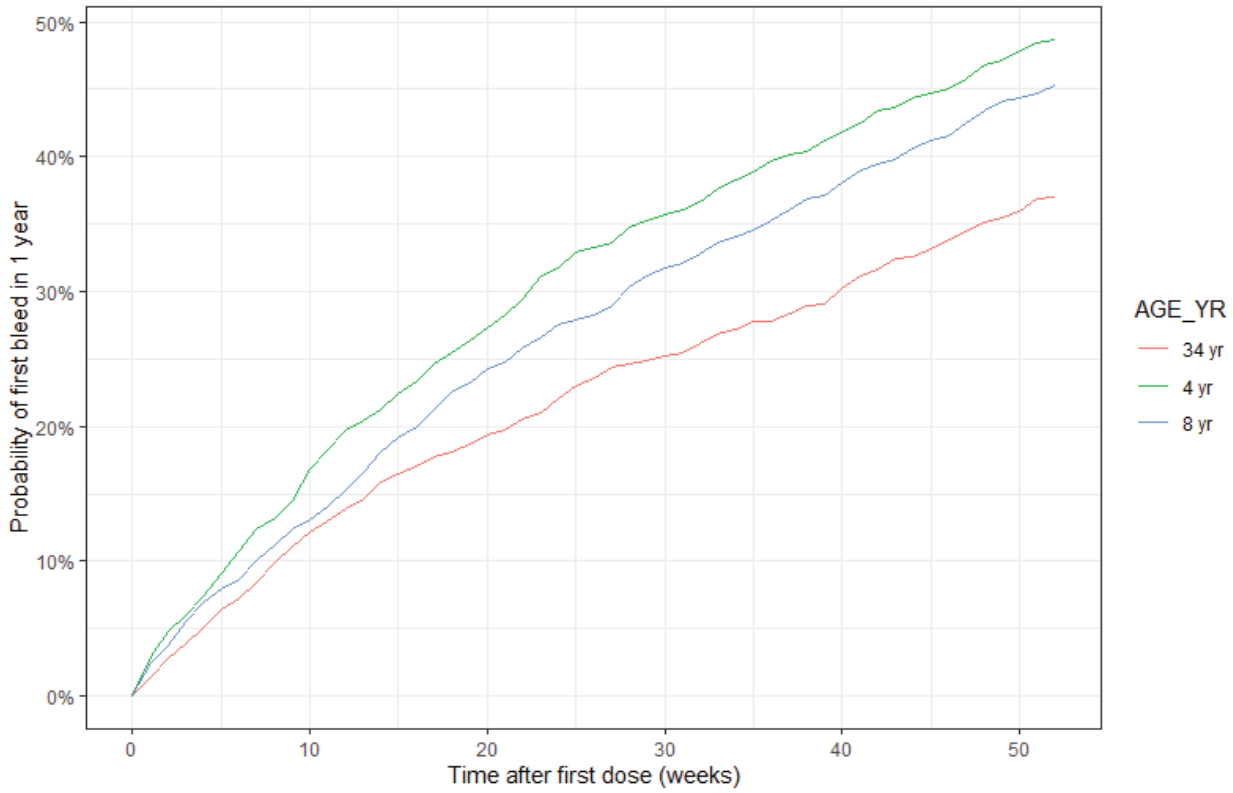
The efficacy impact of a reduced exposure in pediatrics was further evaluated with the RTTE model. Since the RTTE model was developed with adult and adolescent data, there is uncertainty of PK/PD relationship in pediatric patients younger than 12 years. Therefore, the

PK/PD analysis (extrapolation) in pediatrics was evaluated together with other clinical evidence to support the dose proposed for pediatric patients younger than 12 years.

5.1.1 Extrapolated probability of first bleed in 1 year in pediatrics 6-<12 years and <6 years

The half-life in pediatrics is shorter than adults and adolescents, which results in a faster reduction in FVIII activity during a dosing interval and less time above FVIII targets for 50 IU/kg ALTUVIIIO dose. Based on simulations for the proposed prophylactic dosage (50 IU/kg ALTUVIIIO weekly) in typical subjects of different age cohorts using the RTTE model, the probabilities of first bleed in 1 year are predicted to be 45% [95% CI: 39%-50%] and 48% [95% CI: 42%-54%] for pediatrics 6-<12 years and <6 years, respectively (**Figure *1***). Simulation was also conducted for virtual patient population using NHANES 2017-2020 pre-pandemic data. In pediatrics including age down to birth, the predicted ABRs are 0.97 (±1.69) and 1.37 (±2.46) in 6-<12 years and <6 years, respectively. If the lower bound of pediatric age is increased to 1 year to match the lowest age in the XTEND-Kids, the predicted ABR for 1-<6 years age cohort is 1.28 (±2.46).

Figure 1. Probability of First Bleed in 1 Year by Age Group (Typical Subject)



Source: FDA's analysis based on the RTTE model. The typical subject: adult and adolescent patient of 34 years weighing 78 kg, pediatric patient of 8 years weighing 33 kg for 6-<12 years age cohort, and pediatric patient of 4 years weighing 18 kg for <6 years age cohort. 1000 simulation per a typical subject was conducted with weekly intervals.

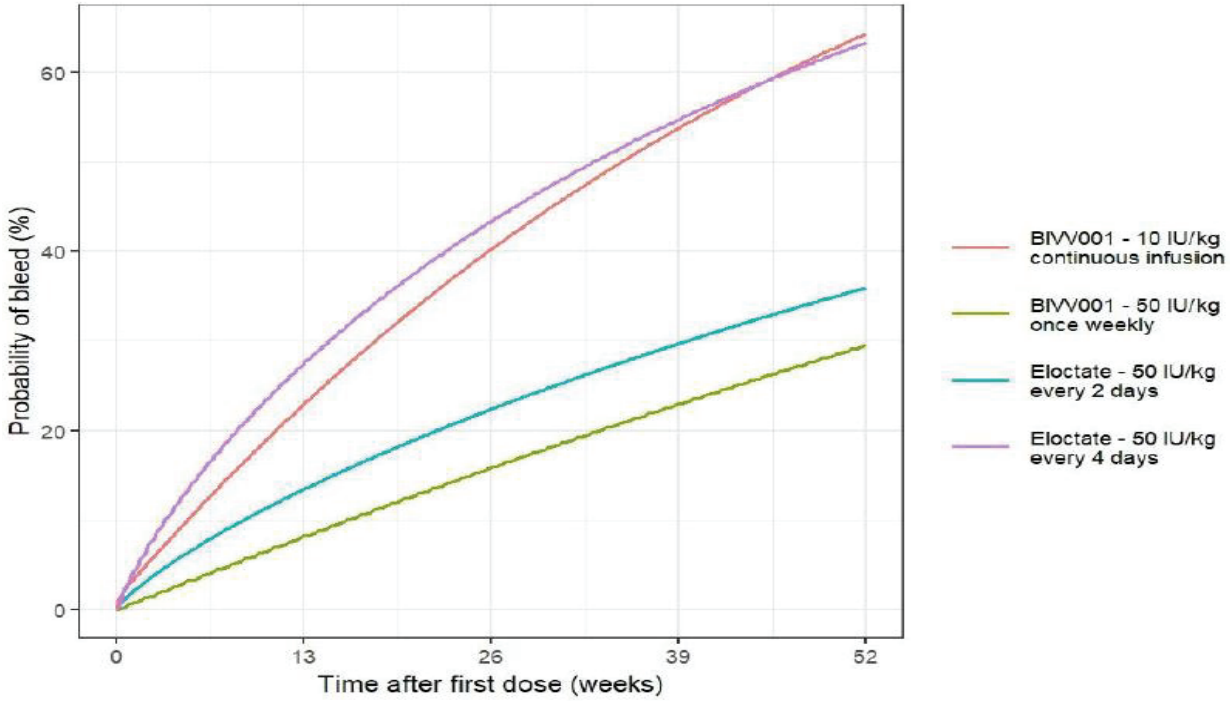
5.1.2 Comparison of Bleeding Risk with Eloctate Treatment

Eloctate, a recombinant fusion protein containing FVIII, is an approved product with an extended half-life that is however substantially shorter than ALTUVIIIO (19 hours vs 48 hours in adults). A similar RTTE model was developed using the PK and bleeding events data from Phase 1~3 studies of Eloctate and corroborate a comparable PK and PD relationship as ALTUVIIIO (**Figure *2***).

For the approved prophylactic dosage of Eloctate (50 IU/kg every 4 days), the bleeding risk is predicted to be approximately the same as when FVIII activity is constantly maintained at ~10 IU/dL with either ALTUVIIIO or Eloctate infusion. This dosage of Eloctate is not optimal for bleeding prevention. The dosage of 50 IU/kg every 2 days could further reduce the bleeding risk, but the dosing frequency is perhaps not ideal in clinical practice. For routine prophylaxis, ALTUVIIIO of 50 IU/kg once weekly is expected to achieve similar efficacy as Eloctate of 50 IU/kg every 2 days.

When assessing the bleeding risk in pediatrics, the probability of first bleed in 1 year (64% [95% CI: 52%-74%]) for a typical adult patient treated with 50 IU/kg Eloctate every 4 days (ABR of 1.6 on a population level) could be considered as an accepted treatment goal for an approved therapy. Compared to this goal, in pediatrics treated with the proposed ALTUVIIIO dose, the probabilities of first bleed in 1 year for typical pediatric patients and the ABRs for pediatrics < 12 years are lower (***Section 5.1.1***), suggesting that the predicted efficacy in pediatrics is not worse than the current standard-of-care. Notably, Eloctate is approved for use in pediatric patients. The prophylactic dose for pediatrics is the same as adults except a slight intensification in those < 6 years (a dosing interval of 3.5 days) which does not bring FVIII activity to the adult level. This indicates 1) the treatment goal attained in adults is more conservative than pediatrics for Eloctate, and 2) pediatric dose of Eloctate appears sufficient based on years of clinical practice. These together provide assurance that the proposed pediatric ALTUVIIIO dose would be adequate for bleeding prevention despite a shortened duration above FVIII targets compared to adults.

Figure 2. Probability of First Bleed (%) with Time over 52 Weeks for Various Dosages of ALTUVIIIO and Eloctate



Source: Applicant's summary of clinical efficacy (Figure 3). Eloctate PK/PD analysis was not reviewed (data not submitted).

5.1.3 Interim annualized bleeding rate (ABR) in XTEND-Kids

For the ongoing study in the pediatric patients < 12 years with prophylactic treatment with ALTUVIIIO (50 IU/kg weekly), selected secondary efficacy endpoints were summarized by age cohort by the data cutoff date of 01/24/2022. Prior to study entry, all patients except one in older cohort (6-<12 years) were on prophylactic treatment of FVIII replacement therapy (e.g., Eloctate), predominantly with twice per week (30 [46%]) or 3 times per week (17 [26%]) posology, and majority of them (44 [66%]) had a stable duration of pre-study prophylactic regimen longer than 12 months.

In the interim analysis, the mean duration of ALTUVIIIO dosing was 19 weeks overall (range: 0.9 to 44.1 weeks) with 19 doses on average. For ABR with an efficacy period of at least 26 weeks, data from 23 out of 67 enrolled patients were included in the summary. Nine (82%) in <6 years age cohort and 8 (67%) in 6-<12 years age cohort had ABR of 0, the percentage of which aligns with adult and adolescents (86 [65%]). Therefore, the interim data support the proposed dosage of 50 IU/kg weekly in pediatrics younger than 12 years.

In summary, the bleeding prevention in pediatrics younger than 12 years is predicted to be better than the accepted treatment goal of an approved FVIII replacement therapy. The observed interim efficacy data of pediatrics also is in alignment with clinical data of adults and

adolescents. These pieces of evidence suggest that 50 IU/kg weekly is adequate for the control and prevention of bleeding in pediatrics.

6. APPENDICES

6.1 Population Pharmacokinetic Analyses

5.1.1 PopPK model

The objective of popPK analysis was to develop a popPK model using plasma one-stage FVIII activity data to assess sources of variability (intrinsic and extrinsic covariates) of ALTUVIIIO in adult and pediatric patients with hemophilia A.

The popPK model for ALTUVIIIO included 260 subjects with 3054 evaluable post-dose FVIII activity records pooled from 2 Phase 1/2a and 3 Phase 3 (XTEND-1, EXTEND-Kids, LTS16294) studies. Post-doc BLQ accounted for 2.88% of all post-dose FVIII activity samples and was excluded in the analysis. A summary of the demographics and selected baseline lab assessments included in the popPK analysis was provided in **Table *4*** and **Table *5***. A total of 61 pediatric patients with age ranging from 1 to 17 years old was included in the popPK analysis.

The popPK analysis was conducted by the applicant using (b) (4) and evaluated by the reviewer. The PK of ALTUVIIIO was characterized by a one-compartment model with linear elimination and a proportional and additive error model. The endogenous levels of FVIII at baseline is very low for severe hemophilia A (<1 IU/dL) and thus unlikely to affect PK of exogenous FVIII. Between-subject variability (BSV) was included on CL and V. A stepwise covariate modeling approach was implemented to investigate the effects of covariate on ALTUVIIIO. For this analysis, a forward inclusion (p-value < 0.01) and backward elimination (p-value < 0.001) procedure was used.

Parameter estimates of final model were provided in **Table *6***. The goodness of fit plots of model evaluation was presented in **Figure *3***. The diagnostic plots suggested the model fitted the data with good precision and minimal bias in general. Visual predictive check also showed that the final model described the observed PK profile of ALTUVIIIO in both adult and pediatric patients with hemophilia A reasonably well (**Figure *4***).

Weight is a statistically significant covariate on both CL and V. Patients with lower body weight are expected to have a lower CL and V. Noting that dose is linearly scaled by body weight whereas CL and V are not, exposure thus increases with increasing weight. In pediatrics, weight grows congruently with age. Simulation results suggest the overall exposure of ALTUVIIIO at steady state was lower in pediatrics <12 years than adolescents and adults receiving the same 50 IU/kg dose. The duration with FVIII activity above 10 IU/dL, 20 IU/dL, and 40 IU/dL was shorter in pediatrics <12 years, especially those <6 years (**Figure *5***).

Asian race (N=40) is identified to have a reduced CL compared to other races including White (N=177), Black (N=5) and other/unreported (N=38). Covariates such age, hepatitis C/HIV infection status, or blood type had no significant effect on ALTUVIIIO PK.

The steady state exposure of ALTUVIIIO administered weekly in 32 pediatric (XTEND-Kids) and 149 adult (XTEND-1) patients was predicted based on post-hoc PK parameters from final PK model. All age group cohorts except pediatrics <6 years showed good agreement in PK parameter estimates between posthoc and NCA analyses. For pediatrics < 6 years, post-hoc Cmax was about 23% lower than observed Cmax, suggesting a mild age effect in young pediatrics on V. This effect is not considered clinically meaningful.

Table 4. Baseline Characteristics of Subjects in the PK Analysis Dataset (Continuous Variables)

Covariate candidate	Descriptive statistic	EFC16293 (N=159)	EFC16295 (N=61)*	TDR16219 (N=24)	TDU16220 (N=15)	All studies (N=260)‡
Baseline bodyweight (kg)	Mean (SD)	78.5 (19.1)	28.0 (13.4)	89.3 (21.7)	80.2 (14.3)	67.6 (28.5)
	Median (5th - 95th percentile)	78.0 (48.7-114)	23.5 (13.5-56.6)	88.6 (55.1-125)	79.5 (61.0-102)	72 (17.5-113)
Baseline age (year)	Mean (SD)	35.4 (15.1)	6.35 (2.92)	38.4 (9.68)	39.4 (13.9)	29.0 (17.9)
	Median (5th - 95th percentile)	35.0 (13.9-61.1)	6.00 (2.00-11.0)	37.5 (25.2-54.4)	36.0 (21.1-62.3)	30.0 (4.00-60.0)
Baseline hematocrit (%)	Mean (SD)	43.2 (3.54)	36.4 (2.53)	43.3 (3.80)	44.5 (3.36)	41.7 (4.47)
	Median (5th - 95th percentile)	43.0 (37.0-48.0)	36.0 (33.0-41.0)	43.0 (38.0-49.0)	45.0 (39.7-49.3)	42.0 (34.0-48.0)
Baseline VWF (IU/dL)†	Mean (SD)	117 (42.8)†	78.9 (27.4)	139 (58.0)	149 (64.9)	112 (47.2)
	Median (5th - 95th percentile)	105 (57.0-188)†	70.0 (49.0-130)	136 (66.0-246)	132 (80.8-271)	100 (53.0-188)

† One patient in EFC16293 has a baseline VWF > ULOQ (>597 IU/dL). This patient was excluded from summary statistics for Baseline VWF.

‡ One patient who was not in EFC16293 was included from LTS16294, who had baseline bodyweight of 45 kg, baseline age of 13 years, baseline hematocrit of 47% and baseline VWF of 112 IU/dL.

* One patient from EFC16295 was excluded in model development due to lack of dosing information and summary statistics for EFC16295 are computed excluding this patient.

Source: Applicant's PopPK report (Table 4)

Table 5. Baseline Characteristics of Patients in the PK Analysis Dataset (Categorical Variables)

Study	N	Covariate	Type	n (%)
All	260	Gender	Female	1 (0.4)
			Male	259 (99.6)
All	260	Age group	Adult (18 years ≤Age)	173 (66.5)
			Adolescent (12 years ≤Age<18 years)	26 (10)
			Older pediatric (6 years ≤Age<12 years)	35 (13.5)
			Younger pediatric (Age<6 years)	26 (10)
All	260	Hepatitis C infection status	With	76 (29.2)
			Without	184 (70.8)
All	260	HIV infection status	With	24 (9.2)
			Without	236 (90.8)
All	260	Race	Caucasian	177 (68.1)
			Asian	40 (15.4)
			Black	5 (1.92)
			Other race	8 (3.08)
			Race not reported	30 (11.5)
All	260	Blood type	Blood type A	77 (29.62)
			Blood type AB	10 (3.85)
			Blood type B	24 (9.23)
			Blood type O	94 (36.15)
			Blood type unknown	55 (21.15)

Source: Applicant's PopPK report (Table 5)

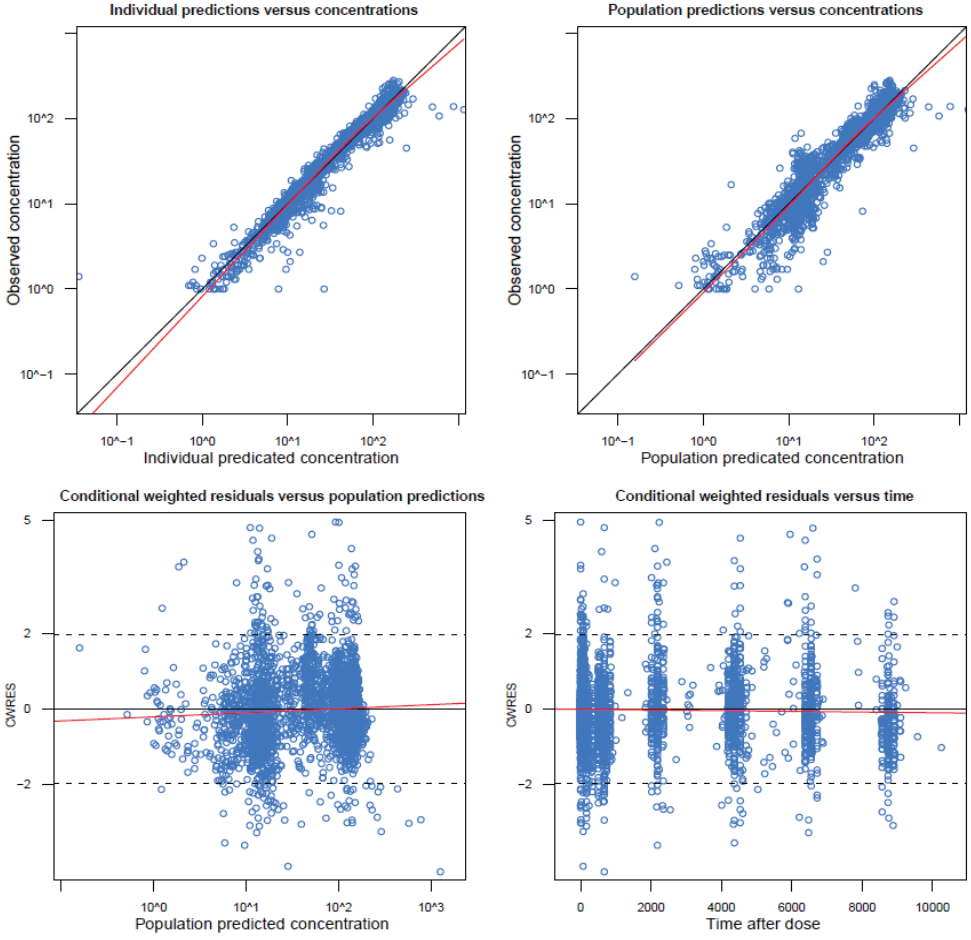
Table 6. Parameter Estimates of the Final PopPK Model for ALTUVIIIO

Parameter	Estimate	Bootstrap Median	Bootstrap [2.5th, 97.5th]
Typical value of CL (θ_1, dL/h)	0.433	0.433	[0.421 ; 0.445]
Typical value of V (θ_2, dL)	30.2	30.2	[29.6 ; 30.8]
Power coefficient of bodyweight on CL	0.677	0.676	[0.614 ; 0.724]
Power coefficient of bodyweight on V	0.791	0.791	[0.744; 0.839]
Proportional coefficient of Asian on CL	0.896	0.898	[0.851 ; 0.941]
Inter-individual variability			
Parameter	**Estimate (%CV)**	**Bootstrap Median**	**Bootstrap [2.5th, 97.5th]**
CL	0.0354 (19.0)	0.0352	[0.0268 ; 0.0491]
V	0.0209 (14.6)	0.0204	[0.0151 ; 0.0268]
Corr-CL-V	0.0148	0.0146	[0.00905 ; 0.0214]
Residual variability			
Parameter	**Estimate**	**Bootstrap Median**	**Bootstrap [2.5th, 97.5th]**
Proportional term	0.182	0.180	[0.163 ; 0.199]
Additive term (IU/dL)	0.837	0.856	[0.455; 1.42]

Abbreviation: CL: clearance from central compartment; V: volume of central compartment; RSE (%): Percentage of Relative Standard Error (100% * SE / Estimate); CI: confidence interval; θ is the population estimate of PK parameter; CV: Coefficient of Variation.

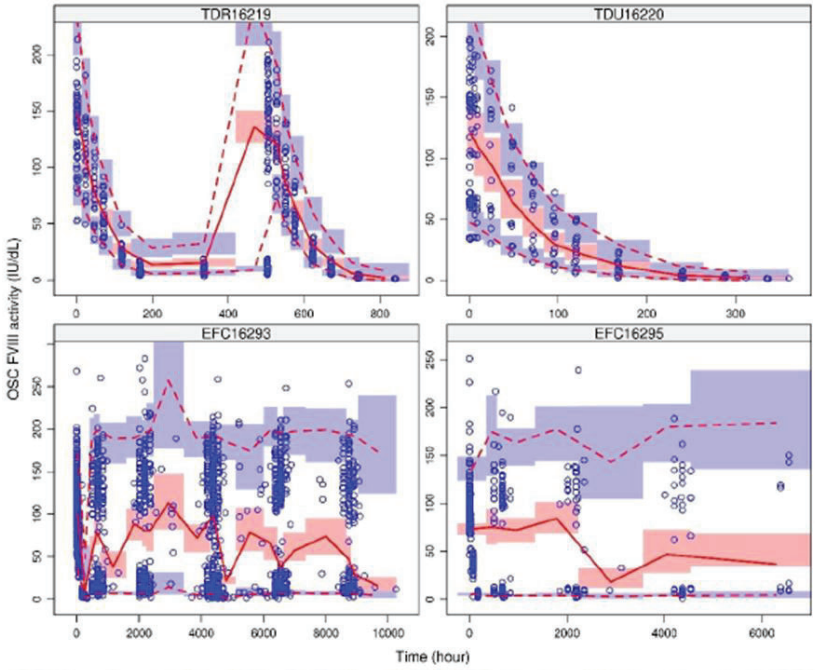
Source: Applicant's PopPK report (Table 13).

Figure 3. Goodness of Fit Plots of the Final Model for ALTUVIIIO



Source: FDA's analysis based on the final popPK model.

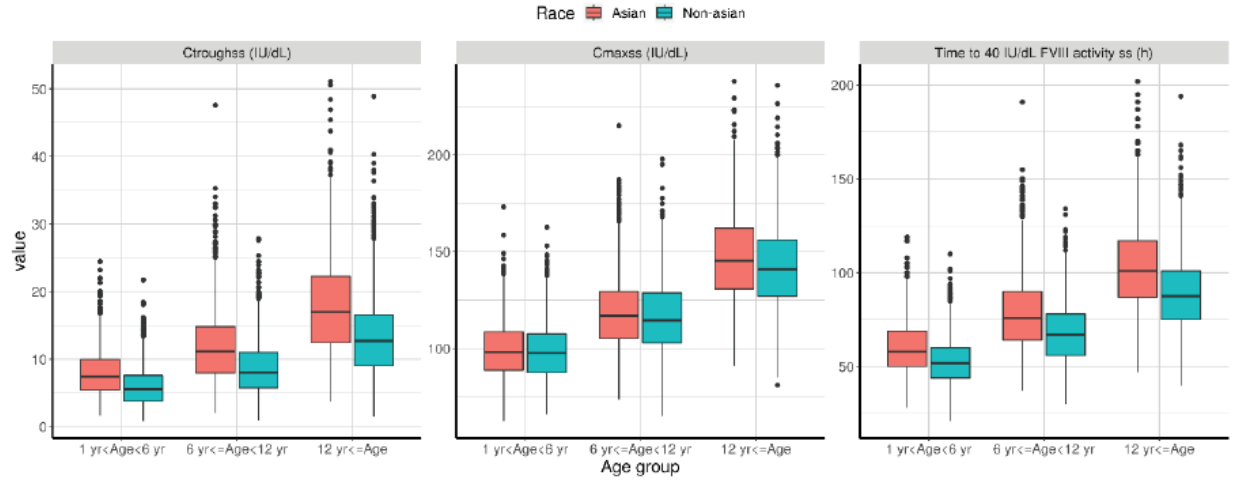
Figure 4. Visual Predictive Checks of ALTUVIIIO Stratified by Study



Legend: Blue open circles show observed data, red solid line shows the model simulated median, red dashed lines show model simulated 5th and 95th percentiles. Pink and blue bands represent 90% CI around simulated median and simulated 5th/ 95th percentiles respectively. For the purpose of VPC, the one unique patient from LTS16294 was considered in EFC16293.

Source: Applicant's PopPK report (Figure 16).

Figure 5. Model Predicted Exposure of ALTUVIIIO at Steady State by Age and Asian Race



Source: Applicant's PopPK report (Figure 22).

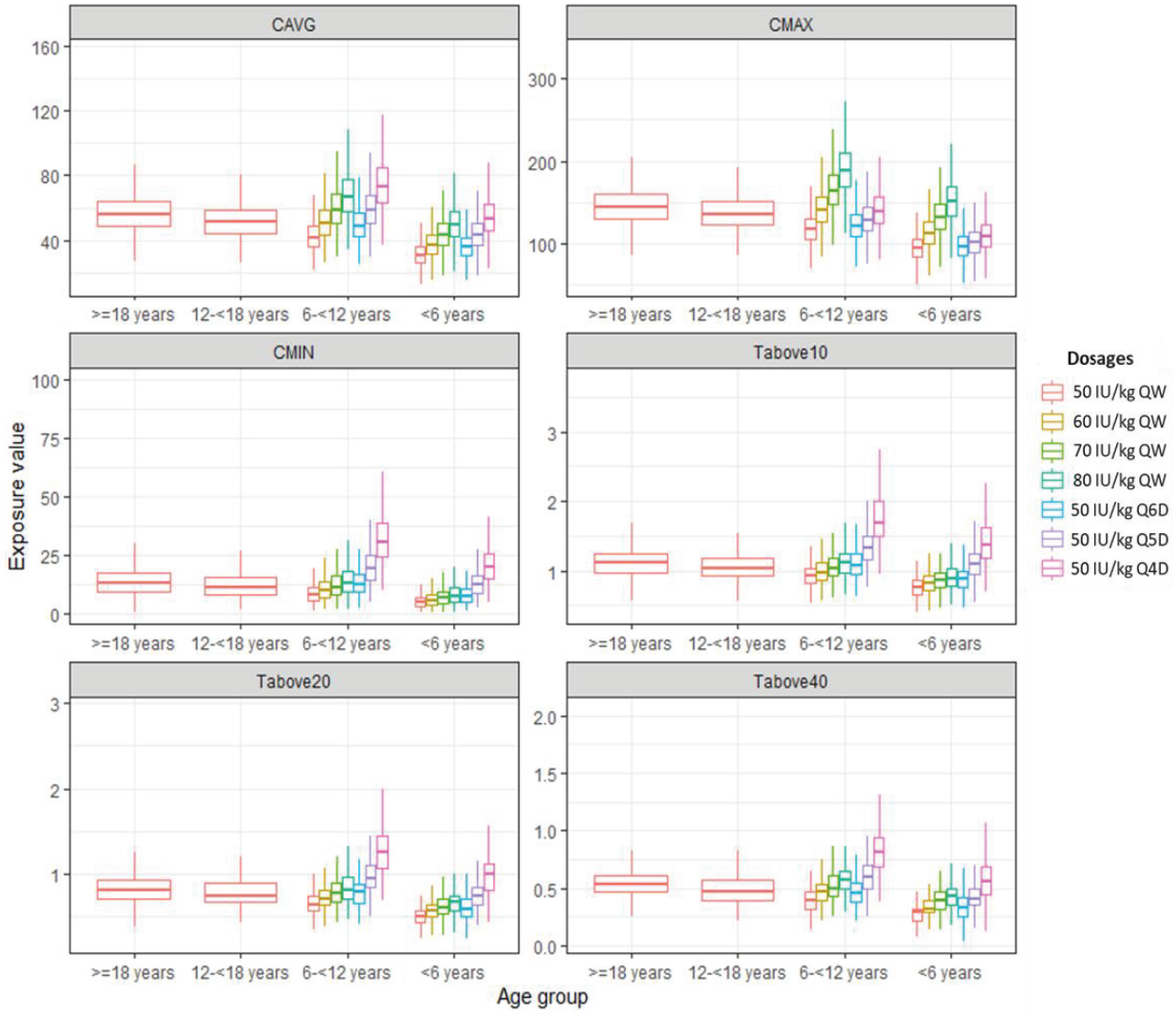
5.1.2 Simulation Analysis with PopPK Model

Pediatrics receiving the same dose are expected to have decreased exposure compared to adults and adolescents. Simulations were conducted to provide alternative dosages that can best match adult exposures.

Simulation based on final popPK model was performed for various dosages in virtual subjects. Adults and adolescents were only simulated for 50 IU/kg weekly dose and their exposures were used as references. In pediatrics 6-<12 years given 50 IU/kg weekly, the reduction in steady-state exposures is minimal and the dose escalation is generally not needed. In pediatrics <6 years given 50 IU/kg weekly, the reduction in all exposures is prominent, and the median fraction of time above FVIII targets (10, 20, 40 IU/dL) for a dosing interval reduces by 32%, 39%, and 46%, respectively, compared to adults.

As shown in **Figure *6***, in pediatrics < 6 years across 7 dosages explored, a higher or more frequent dose such as 80 IU/kg weekly or 50 IU/kg every 5 days can achieve similar exposures as adults and adolescents.

Figure 6. Simulated Steady State Exposures for Various Dosages in Pediatrics < 12 Years



Source: Reviewer's analysis. NHANES 2017-2020 pre-pandemic subject data were used in simulation. QW: weekly, Q6D/Q5D/Q4D: every 6/5/4 days. Tabove10/Tabove20/Tabove40: fraction of time above FVIII activity of 10/20/40 IU/dL for a dosing interval. Y-axis unit is IU/dL for CAVG, CMAX, and CMIN, and unitless for Tabove10, Tabove20, and Tabove40.

6.2 PK/PD Analysis

PK/PD analysis was conducted by the applicant using data from Phase 3 study XTEND-1 to explore the relationship between exposure of ALTUVIIIO and bleeding events and assess the influence of selected intrinsic and extrinsic factors as covariates on bleeding risk in Hemophilia A patients.

The PK/PD dataset include time to event data of adult and adolescent patients and individual PK parameters predicted using popPK model. All bleeding events for the efficacy period were used for development of an RTTE model. Consecutive bleeding occurring within 72 hours or multiple sites of bleeding treated with a single injection was considered a single bleeding episode. A total of 159 subjects with 520 PD records were included in the PK/PD analysis.

The base bleed hazard was well characterized by Weibull base hazard model. The effect of FVIII activity post ALTUVIIIO dosing was parameterized on base hazard using proportional hazard term, which was identified to be statistically significant. Bleeding type (traumatic vs spontaneous bleeds) and bleeding location (joint vs non-joint bleeds) were incorporated in the model via logit function assuming equal probability of bleeding for the dichotomized variables. Treatment arm (prophylaxis vs on-demand) was the only significant covariate retained in the final model by the stepwise criteria for inclusion/exclusion as well as model stability and robustness of parameter estimation. Parameter estimates of the final model were provided in **Table *7***. Visual predictive check showed that the final model described the bleeding events in both adult and adolescent patients with hemophilia A treated with prophylactic or on-demand ALTUVIIIO reasonably well (**Figure *7***).

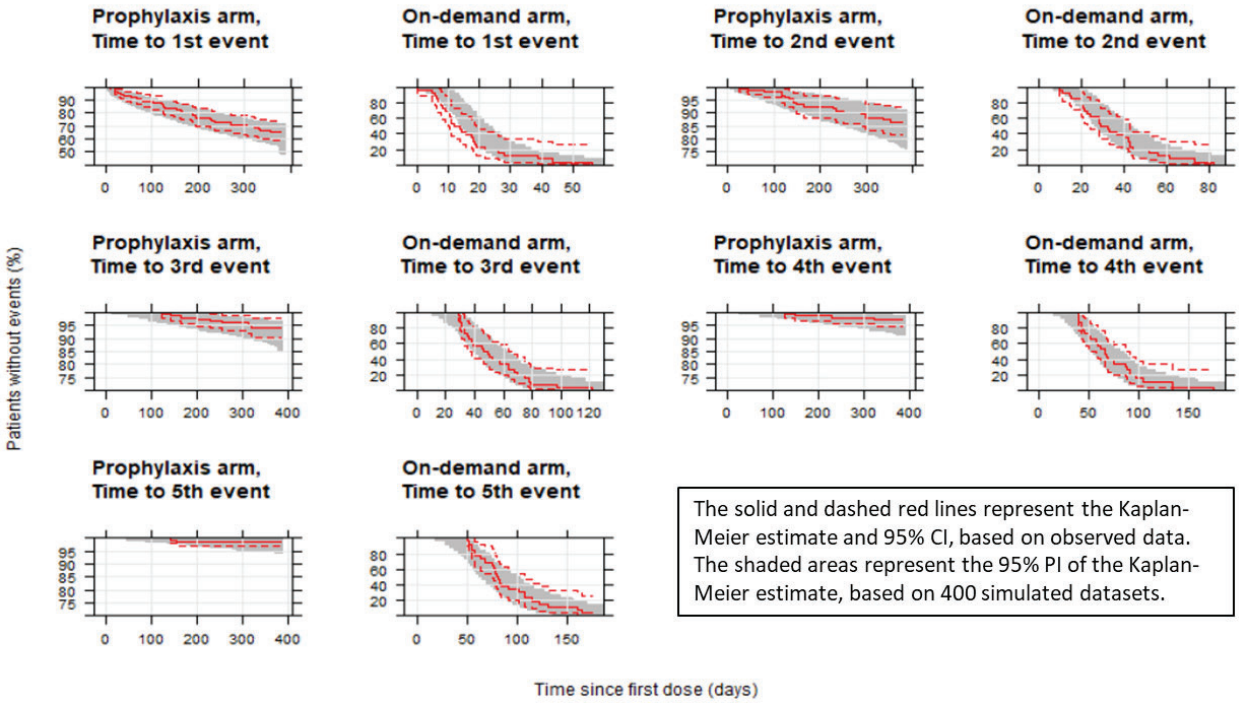
Table 7. Parameter Estimates of the Final RTTE Model

Parameter	Unit	Estimate	SIR 95% CI	RSE (%)	SHR (%)
Constant of the base hazard (λ)	$hour^{-1}$	0.00247	0.00112:0.00508	36	-
Shape parameter of the base hazard (γ)	-	1.02	0.900:1.16	6	-
Constant of the drug effect (β)	$(IU/dL)^{-1}$	-1.73	-2.35 : -1.24	15	-
Shape parameter of the drug effect (α)	-	0.247	0.191:0.311	11	-
On-demand arm effect on the base hazard	-	2.21	1.58:2.90	14	-
IIV Base hazard	CV (%)	114	87.3:147	13	33

OFV: objective function value; SIR: sampling importance resampling, CI: confidence interval; RSE: relative standard error from NONMEM; SHR: shrinkage on standard deviation scale; CV: coefficient of variation

Source: Applicant's Repeated time to event analysis report (Table 11).

Figure 7. Visual Predictive Check of the Final RTTE Model



Source: Applicant's Repeated time to event analysis report (Figure 10).

6.3 Physiologically based Pharmacokinetic (PBPK) Modeling and Simulation Review

The dose selection in pediatric patients aged <12 years for the Phase 3 study XTEND-Kids was also supported by PBPK modeling and simulation analysis. The objective of the Applicant's PBPK analysis (Report PBM0083) was to predict FVIII levels, especially in the youngest population, and identify a pediatric dosing regimen that would yield the target FVIII activity levels over the dosing interval.

The objective of this review is to provide an overview of the Applicant's PBPK modeling effort to support dosing for the pediatric development program of ALTUVIIIO.

6.3.1 Model Development

The PBPK analysis was conducted using the PBPK software (b) (4) .

Eloctate PBPK model

A PBPK model was first developed and verified for the recombinant FVIII Fc fusion protein Eloctate (an antihemophilic FVIII) using observed adult and pediatric PK data for Eloctate in subjects with Hemophilia A. The objective of Eloctate model was to assess the feasibility of modeling approach for Fc fusion proteins as FVIII factor replacement therapies.

A minimal PBPK model for monoclonal antibody (mAb) was used to describe the distribution and clearance of Eloctate, including Neonatal Fc Receptor (FcRn) recycling pathway. The equilibrium dissociation constant for FcRn binding (KD= (b) (4)) was derived from in vitro

data (EC50 of Eloctate and human IgG1 using (b) (4) measurement). The values of (b) (4) rate ((b) (4)), recycling rate of FcRn bound Fc FVIII (Krc= (b) (4)), and catabolic clearance of Fc FVIII from (b) (4) (CLcat=(b) (4)) were optimized from observed PK data in adults. The default software values for vascular (σv= (b) (4)) and lymph reflection coefficients (σi= (b) (4)), and recycling fraction of FcRn bound Fc FVIII (FR= (b) (4)) were used in the adult model.

ALTUVIIIO PBPK model

A minimal PBPK model for mAbs was used to describe the distribution and clearance of ALTUVIIIO, including FcRn-IgG recycling pathway. The KD value (= (b) (4)) was derived from the in vitro binding affinity assay. The values of (b) (4) , Krc (= (b) (4)), and CLcat (=(b) (4)) were optimized from observed data. The default software values for σv (= 0.62) and σi (= (b) (4)), and FR (=(b) (4)) were used.

Additional comments: The FVIII activity measured in the plasma, using (b) (4) chromogenic or one-stage clotting assay, was used as surrogate for plasma concentrations to assess the PK of Eloctate and ALTUVIIIO. The FVIII activity data generated using chromogenic assay were used for model validation and application. The one-stage clotting assay was later considered the most appropriate method for the assignment of ALTUVIIIO potency by the Applicant. Hence, ALTUVIIIO model was also simulated with optimization of input parameters (i.e., σv= (b) (4) and CLcat=(b) (4)) to characterize the FVIII activity measured by the one-stage clotting assay.

Pediatric PBPK model for Fc fusion proteins

The default software pediatric population model and additional pediatric ontogeny profiles (e.g., IgG concentration, lymphatic flow rate and volume) from the minimal PBPK model for mAb implemented in the software's Biologic module were used for modeling of Eloctate and ALTUVIIIO in pediatrics. In addition, the effects of age on FcRn abundance and vascular reflection coefficient (σv) were optimized, by the Applicant, based on current findings from literature[1] (refer to **Table *10*** for pediatric parameter values).

6.3.2 Model verification

Eloctate PBPK model in adults and pediatrics

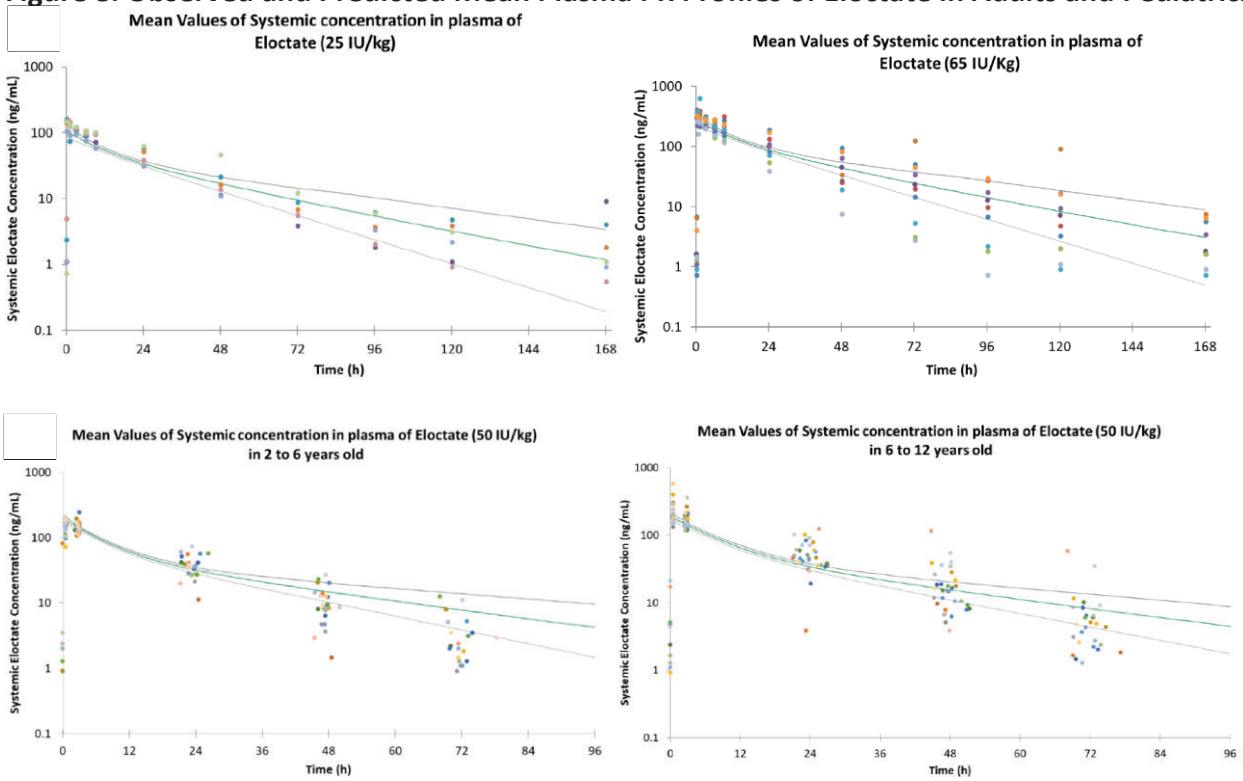
Eloctate model was verified using clinical PK data by comparing predicted with observed values in adult patients following a single IV dose of 25 IU/kg or 65 IU/kg [Study 998HA101] and in pediatric participants (2 to 12 years) following an IV dose of 50 IU/kg [Study 8HA02PED]. Note that for model input, the unit of dose was converted from IU/kg to mg/kg, based on specific activity of 5500 IU/mg.

The predicted and observed PK profiles of Eloctate in adults after a single IV dose of 25 IU/kg or 65 IU/kg are shown in **Figure *8***, panels A and B, respectively. The predicted and observed PK profile of Eloctate in children aged ≥2 to <6 and ≥6 to <12 years following a single IV dose of 50

[1] Hardiansyah D, Ng CM. Effects of the FcRn developmental pharmacology on the pharmacokinetics of therapeutic monoclonal IgG antibody in pediatric participants using minimal physiologically-based pharmacokinetic modelling. MAbs. 2018. 10:1144- 56.

IU/kg are shown in **Figure *8***, panels C and D, respectively. The model predicted the Cmax and AUC values of Eloctate in both adult and pediatric populations with reasonable accuracy (prediction error ≤ ±25%) (**Table *8***).

Figure 8. Observed and Predicted Mean Plasma PK Profiles of Eloctate in Adults and Pediatrics



Source: Figures 4, 5, 6 and 7 of PBPK report pbm0083. Circles: observed data from Study 998HA101 (A and B) and Study 8HA02PED (C and D); green line: Mean population prediction; gray lines: predicted 5th to 95th percentile.

Table 8. Observed and Predicted Mean PK Parameters of Eloctate in Adults and Pediatrics

Population	Age (years)	Eloctate IV Dose	Cmax (ng/mL)			AUC (ng.h/mL)		
			Observed	Predicted	%PE	Observed	Predicted	%PE
Adult	23-61	25 IU/Kg	140	105	-25	3009	2671	-11
		65 IU/Kg	345	272	-21	7794	6944	-11
Pediatric	≥2 to <6	50 IU/Kg	174	196	12	2422	2915	-2
	≥6 to <12	50 IU/Kg	193	188	20	3244	3029	-7

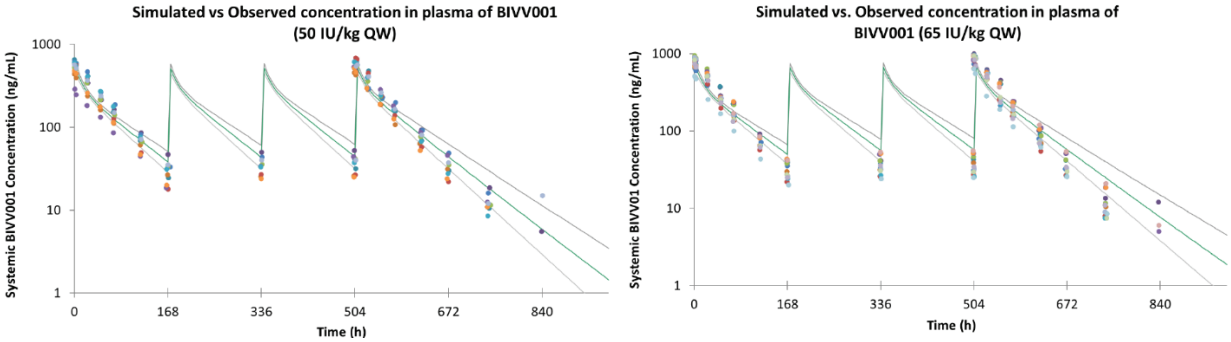
Source: Tables 8 and 9 of PBPK report pbm0083. PK data are mean values. AUC are AUC0-168h. Observed data from Studies 998HA101 and 8HA02PED in adults and pediatrics, respectively.

ALTUVIIIO PBPK model in adults

ALTUVIIIO model for adults was verified using available clinical PK data by comparing predicted with observed values in adult patients following a single IV dose of 25 IU/kg or 65 IU/kg [Study 242HA101] and repeated IV weekly doses of 50 IU/kg or 65 IU/kg [Study 242HA102]. For model input, the unit of dose was converted from IU/kg to mg/kg, based on specific activity of 2000 IU/mg for model input.

The predicted and observed PK profiles of ALTUVIIIO in adults after repeat doses of 50 IU/kg and 60 IU/kg are shown in **Figure *9***. The model predicted the Cmax and AUC values of adult population with reasonable accuracy (prediction error ≤ ±20%) (**Table *9***). The observed and predicted FVIII activity using one-stage clotting assay in the adults after repeated doses of 50 IU/kg of ALTUVIIIO are presented in **Figure *10***.

Figure 9. Observed and Predicted Mean Plasma PK Profiles of ALTUVIIIO in Adults



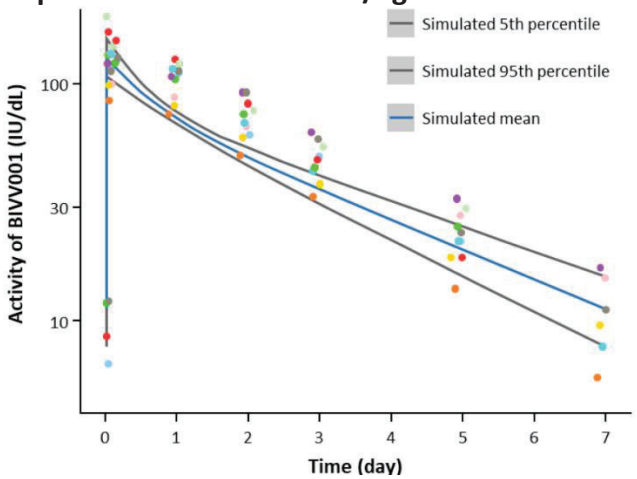
Source: Figures 10 and 11 of PBPK report pbm0083. Circles: individual observed data from Study 242HA102; green line: Mean population prediction; gray lines: predicted 5th to 95th percentile.

Table 9. Observed and Predicted Mean PK Parameters of ALTUVIIIO in Adults

Population	Age (years)	ALTUVIIO IV Dose	Cmax (ng/mL)			AUC (ng.h/mL)		
			Observed	Predicted	%PE	Observed	Predicted	%PE
Adult	19-63	25 IU/Kg SD	282	288	2	14950	13726	-8
		65 IU/Kg SD	735	749	2	43300	35687	-18
	24-58	50 IU/Kg QW	575	620	8	31650	31327	-1
		65 IU/Kg QW	865	806	-7	42400	40724	-4

Source: Tables 10 and 11 of PBPK report pbm0083. PK data are mean values. AUC values are $AUC_{0\text{-}360h}$ for SD and $AUC_{0\text{-}456h}$ for QW (4th dose). Observed data from Studies 242HA101 and 242HA102.

Figure 10. Observed and Predicted FVIII Activity Levels of ALTUVIIIO in Adults Following Repeated IV Doses of 50 IU/kg



Source: Figure 12 of PBPK report pbm0083. Circles: individual observed data from Study 242HA102 at day 22, using one-state clotting assay; blue line: Mean population prediction of factor activity; gray lines: predicted 5th to 95th percentile.

6.3.3 Model Application

ALTUVIIIO PBPK model in pediatrics

ALTUVIIO PBPK model was used to simulate the PK for the proposed dosing scenarios of 50, 65 or 80 IU/kg IV QW in pediatric age groups of 0 to <2, ≥2 to <6, and ≥6 to <12 years.

Pediatric PBPK simulations were conducted with 10 virtual trials of 10 participants/age group in each virtual trial (total n = 100) following ALTUVIIIO IV QW doses of 50, 65 or 80 IU/kg for 4 weeks (corresponding doses of 0.025, 0.0325 and 0.04 mg/kg, respectively, were used as dose input based on the conversion factor of 2000 IU/mg). The demographics for the virtual population, and optimized input parameters for age-related adjustment of FcRn concentration and vascular reflection coefficient (σv) are shown in **Table *10***. The predicted FVIII activity profiles and PK parameters for multiple dosing of ALTUVIIIO (at Day 22) in the pediatric groups are shown in **Table *11*** and **Figure *11***.

Table 10. Demographics and Ontogeny Parameters for the Virtual Pediatric Population

Age (year)		Body weight (kg) Mean (Median)	FcRn Concentration (μM) Mean (CV%)	σ_v [a]
Range	Mean (median)			
0 to 2 years	1.08 (1.06)	10.2 (9.92)	44.8 (25.3)	0.046
2 to 6 years	4.16 (4.13)	17.3 (16.8)	42.9 (24.1)	0.192
6 to 12 years	9.23 (9.19)	28.5 (26.9)	45.6 (24.2)	0.387

Source: Table 7 of PBPK report pbm0083.

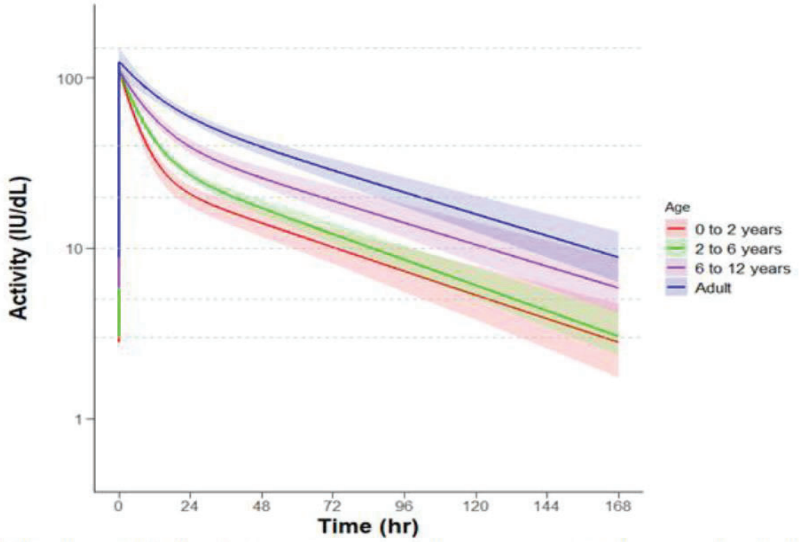
Table 11. PBPK Predicted PK Parameters of ALTUVIIIO at Steady State After Once Weekly Dosing in Pediatrics

Age cohort (years)	Dose (IU/kg)	C_{max} (IU/dL)	C_{trough} (IU/dL)	C_{avg} (IU/dL)
0 to <2	50	110 [109,111]	2.64 [2.50,2.79]	13.4 [13.1,13.6]
	65	143 [141,145]	3.43 [3.25,3.62]	17.4 [17.1,17.7]
	80	175 [173, 177]	3.58 [3.42, 3.74]	20.4 [20.1, 20.7]
≥2 to <6	50	110 [109,111]	2.97 [2.88,3.07]	16.1 [15.9,16.2]
	65	143 [141,144]	3.86 [3.74,3.99]	20.9 [20.7,21.1]
	80	176 [174,177]	4.76 [4.60,4.91]	25.7 [25.5,26.0]
≥6 to <12	50	109 [107,110]	5.63 [5.40,5.87]	22.9 [22.5,23.2]
	65	141 [140,143]	7.32 [7.02,7.63]	29.7 [29.2,30.2]
	80	174 [172,176]	9.01 [8.65,9.38]	36.6 [36.0,37.2]

Abbreviations: C_{max} – maximum concentration at steady state, C_{trough} - predose concentration during repeated dosing, C_{avg} – average concentration at steady state.

Source: Table 12 of PBPK report pbm0083. PK data are geometric means [90% confidence intervals]. Cavg= average weekly concentration, calculated as $AUC_{0\text{-}168h}$/168). PK parameter units were converted to IU/dL from predicted values in mass per volume units.

Figure 11. PBPK Predicted Plasma PK Profiles of ALTUVIIIO at Steady State After 50 IU/kg QW in Adults and Pediatrics



Note: PBPK model predicted PK profile by specific age groups and doses. The simulated PK profiles reflects the FVIII activity measured by chromogenic assay. Solid lines represent mean response; shaded regions represent 90% prediction intervals; horizontal dashed lines (from the top) represent concentrations of 150 IU/dL, 40 IU/dL, 20 IU/dL, 10 IU/dL, 5 IU/dL and 3 IU/dL.

Source: Figure 13 of PBPK report pbm0083.

PBPK simulations indicated that the dose regimen of ALTUVIIIO 50 IU/kg IV QW would maintain the pediatric population below the upper physiological limit of FVIII activity levels of 150 IU/dL. Cmax values were predicted to be similar across age groups.

The 50 IU/kg IV QW regimen would maintain mean FVIII activity levels >10 IU/dL for 2-5 days in children aged <12 years. The Cavg values were predicted to be around 13, 16, and 23 IU/dL for children aged 0 to <2, ≥2 to <6, and ≥6 to <12 years, respectively. FVIII activity levels >5 IU/dL (mild hemophilia A range) would be maintained at the end of the dosing interval only in children aged ≥6 to <12 years. The Ctrough values were predicted to be around 2.6, 3.0, and 5.6 IU/dL for children aged 0 to <2, ≥2 to <6, and ≥6 to <12 years.

Refer to ***Appendix 6.1*** and ***6.2*** for the clinically relevant metrics of FVIII activity levels for PD and efficacy response in pediatric populations.

6.3.4 Conclusions

- PBPK modeling analysis of recombinant Factor VIII Fc fusion protein was developed for Eloctate and ALTUVIIIO by incorporating distribution and clearance mechanisms, and ontogeny factors to enable extrapolation of PK from adults to pediatrics.
- In children aged <12 years, the ALTUVIIIO dosing regimen of 50 IU/kg IV QW was predicted to maintain FVIII activity levels >10 IU/dL for 2-5 days and achieve mean FVIII activity levels between 2.6-5.6 IU/dL at trough.
- The PBPK predictions for FVIII activity levels appeared to be lower than those estimated by popPK analyses for children aged <12 years (prospective predictions and interim analysis results from XTEND-Kids). Refer to ***Appendix 6.1*** for popPK analysis of pediatric data.

- The Applicant acknowledged that there is limited knowledge of ontogeny effects on distribution and clearance of Fc fusion proteins. Thus, the PK predictions based on PBPK analysis should be taken with caution and were used as supplementary support for pediatric dose selection for the phase 3 study.